671. *The Alkaline Hydrolysis of Glucose Nitrates.*

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The alkaline hydrolysis of a series of mono-, di-, and tri-nitrates of methyl β-D-glucoside has been studied. The results can be interpreted in terms of the currently accepted mechanisms of nitrate hydrolysis.

BAKER and EASTY [1] and Cristol, Franzus, and Shadan [2] have shown that three types of reaction are involved in the alkaline hydrolysis of nitrate esters, *viz.*, nucleophilic substitution (S_N2), β-hydrogen elimination ($E2$), and α-hydrogen elimination (E_{CO}). The last reaction yields a carbonyl compound and inorganic nitrite, while in the other reactions nitrate is the only inorganic product. Thus, the amount of nitrite released is a measure of the extent of the E_{CO} reaction.

The work of Gladding and Purves [3] suggests that, in the alkaline hydrolysis of certain glucose mononitrates, the E_{CO} reaction occurs to only a slight extent, the S_N2 reaction predominating. Later studies by Ansell and Honeyman [4] and by Honeyman and Morgan [5] support this view.

With glucoside 2 : 3-dinitrates, however, Honeyman and Morgan [5] observed considerable degradation with liberation of inorganic nitrite, and in the case of methyl 4 : 6-*O*-benzylidene-α-D-glucoside 2 : 3-dinitrate they obtained evidence of the formation of an α-diketone. Their results indicate that the nitrate groups on $C_{(2)}$ and $C_{(3)}$ are eliminated largely by the E_{CO} mechanism, although, from the products isolated, it is clear that the S_N2 reaction also occurs to some extent. In the hydrolysis of alkyl D-glucoside 2 : 3 : 4 : 6-tetranitrates Shepherd [6] has shown that the E_{CO} reaction predominates.

Thus it is evident that various factors, *e.g.*, the degree of nitration and the nature of other substituents, affect the extent of the E_{CO} reaction in the alkaline hydrolysis of glucose nitrates, and in view of the supposed pharmacological significance of nitrite release associated with such hydrolysis, the experiments summarised in Tables 1—5 have now been carried out.

The results show that with mononitrates the amount of nitrite released is relatively small, but as the number of nitrate groups is increased (Tables 2—5), there is a very marked increase in the extent of the E_{CO} reaction. Substitution of free hydroxyl by ethylidene groups (Tables 1 and 2) or methyl groups (Table 2) increases the extent of the E_{CO} reaction, especially with methyl β-D-glucoside 2 : 3-dinitrate.

The results in Tables 1, 2, and 3 indicate that, in the hydrolysis of acetates of these mono- and di-nitrates, the acetate groups are removed before the nitrate groups, since considerable amounts of alkali are consumed before any inorganic nitrite appears in the

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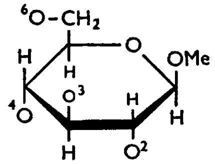
[1] Baker and Easty, *J.*, 1952, 1193.
[2] Cristol, Franzus, and Shadan, *J. Amer. Chem. Soc.*, 1955, **77**, 2512.
[3] Gladding and Purves, *ibid.*, 1944, **66**, 76.
[4] Ansell and Honeyman, *J.*, 1952, 2778.
[5] Honeyman and Morgan, *J.*, 1955, 3660.
[6] Shepherd, *J.*, 1953, 3635.

reaction mixture; this is not surprising in view of the widespread application of the Zemplén technique for the preferential deacetylation of sugar acetate nitrates. With monoacetate trinitrates (Tables 4 and 5) the removal of acetate and nitrate groups does not occur in controlled stages, this being consistent with Bell and Synge's failure to obtain

TABLE 1. *Hydrolysis of methyl β-D-glucoside mononitrates.*



Substituents 2	3	4	6	Conditions		NaOH used	NO_2^- formed
						(Equivs. per mole of ester)	
H	NO_2	H	H	15°,	1 hr.	0	—
				,,	2 hr.	0	—
				B. p.,	2 hr.	0·95	$3·7 \times 10^{-3}$
				,,	,,	0·97	$4·4 \times 10^{-3}$ [a]
Ac	NO_2	Ac	Ac	15°,	1 hr.	2·17	—
				,,	2 hr.	2·17	—
				,,	5 hr.	3·01	—
				,,	7 hr.	3·50	8×10^{-5}
				,,	32 hr.	—	3×10^{-3}
				B. p.,	2 hr.	4·00	$4·3 \times 10^{-3}$
Ac	NO_2	Acx [b]	Ac	15°	1 hr.	1·65	—
				,,	4 hr.	3·03	$2·0 \times 10^{-3}$
				B. p.,	2 hr.	4·03	$5·7 \times 10^{-3}$
H	NO_2	-CHMe-		15°,	1 hr.	0	—
				,,	2 hr.	0	$1·6 \times 10^{-3}$
				B. p.,	2 hr.	0·81	$9·8 \times 10^{-2}$
Ac	NO_2	-CHMe-		15°,	1 hr.	0·56	—
				,,	2 hr.	0·72	$1·6 \times 10^{-3}$
				B. p.,	2 hr.	1·86	$8·0 \times 10^{-2}$
Ac	Ac	NO_2	Ac	15°,	1 hr.	1·80	—
				,,	2 hr.	2·00	—
				,,	28 hr.	—	$9·9 \times 10^{-3}$

[a] 0·26 equiv. of NO_3^- formed. [b] Acx = 1-acetoxyethyl.

TABLE 2. *Hydrolysis of methyl β-D-glucoside 2 : 3-dinitrate and its derivatives.*

Substituents 2	3	4	6	Conditions		NaOH used	NO_2^- formed
						(Equivs. per mole of ester)	
NO_2	NO_2	H	H	15°,	1 hr.	0	—
	(m. p. 99—100°)			,,	2 hr.	0	$3·0 \times 10^{-2}$
				B. p.,	2 hr.	2·50	0·89
NO_2	NO_2	H	H	15°,	1 hr.	0	—
	(m. p. 106—107°) [a]			,,	2 hr.	0	$3·1 \times 10^{-2}$
				B. p.,	2 hr.	2·80	0·92 ff
NO_2	NO_2	Ac	Ac	15°,	1 hr.	0·70	$4·3 \times 10^{-2}$
				,,	2 hr.	1·80	$6·3 \times 10^{-2}$
				B. p.,	2 hr.	4·56	0·95
NO_2	NO_2	Acx [b]	Ac	15°,	1 hr.	1·37	$4·7 \times 10^{-2}$
				,,	2 hr.	1·82	$5·0 \times 10^{-2}$
NO_2	NO_2	Me	Me	15°,	1 hr.	0·26	0·21
				,,	2 hr.	0·30	0·32
				,,	12 hr.	—	0·80
				,,	24 hr.	—	1·18
				,,	36 hr.	—	1·42
				,,	60 hr.	2·00	1·60
NO_2	NO_2	-CHMe-		15°,	1 hr.	0·47	0·36
				,,	2 hr.	0·73	0·43
				,,	4 hr.	0·94	0·61
				22°,	2 hr.	1·00	0·9 [c]
				B. p.,	2 hr.	2·74	1·66

[a] O'Meara and Shepherd.[8] [b] Acx = 1-acetoxyethyl. [c] 40% of starting material recovered.

preferential deacetylation of methyl 6-*O*-acetyl-β-D-glucoside 2 : 3 : 4-trinitrate;[7] indeed the results in Table 4 show that this compound undergoes preferential denitration rather than deacetylation. In the case of methyl 2-*O*-acetyl-β-D-glucoside 3 : 4 : 6-trinitrate, however, the hydrolysis is relatively slow, and it is possible by careful control of the conditions to obtain preferential deacetylation to methyl β-D-glucoside 3 : 4 : 6-trinitrate.[8]

If, in the hydrolysis of methyl 4 : 6-*O*-ethylidene-β-D-glucoside 2 : 3-dinitrate, the reaction is interrupted at the stage where one equivalent of alkali has been consumed and one equivalent of inorganic nitrite liberated, approximately half of the original dinitrate can be recovered unchanged. Clearly, under the conditions used here, selective denitration of the 2 : 3-dinitrate to the 3-nitrate does not occur to any great extent, and it is possible that an α-diketone is one of the primary products of hydrolysis as Honeyman and Morgan[5] have already shown in the case of methyl 4 : 6-*O*-benzylidene-α-D-glucoside 2 : 3-dinitrate.

In interpreting these results it is helpful to consider the compounds in Table 1 (with the exception of the 4-nitrate triacetate) and in Tables 2 and 4 as derivatives of methyl β-D-glucoside 3-nitrate. In these compounds the introduction of electron-attracting substituents (*e.g.*, alkoxy or nitrate) into the 2- or 4-position increases the extent of the $E_{\rm CO}$ reaction by facilitating α-hydrogen elimination at $C_{(3)}$. Further, as pointed out by Baker and Easty[9] for nitrates such as ethylene glycol dinitrate in which the nitrate groups are attached to adjacent carbon atoms, a carbonyl group formed on removal of one nitrate group during alkaline hydrolysis, being electron-attracting, will promote $E_{\rm CO}$ elimination of the remaining nitrate group, and this effect may therefore occur with the compounds in Tables 2 and 4.

TABLE 3. *Hydrolysis of methyl* 2 : 3-*di*-O-*acetyl*-β-D-*glucoside* 4 : 6-*dinitrate*.

Conditions	NaOH used (Equivs. per mole of ester)	NO_2^- formed (Equivs. per mole of ester)	Conditions	NaOH used (Equivs. per mole of ester)	NO_2^- formed (Equivs. per mole of ester)
15°, 1 hr.	0·96	—	B. p., 2 hr.	3·15	0·12
,, 2 hr.	1·48	—	,, 4 hr.	3·45	0·44
,, 3 hr.	—	$4{\cdot}67 \times 10^{-3}$			

TABLE 4. *Hydrolysis of methyl* 6-O-*acetyl*-β-D-*glucoside* 2 : 3 : 4-*trinitrate*.

Conditions	NaOH added (Equivs. per mole of ester)	NaOH used	NO_2^- formed	Conditions	NaOH added (Equivs. per mole of ester)	NaOH used	NO_2^- formed
15°, 45 min.	0·96	0·96	0·90 [a]	15°, 45 min.	3·98	3·98	2·41
,, ,,	2·01	2·01	1·42	,, 1 hr.	excess	4·20	2·90
,, ,,	2·97	2·97	1·92	B. p., 2 hr.	,,	4·18	2·70

[a] 20% of starting material unchanged.

TABLE 5. *Hydrolysis of methyl* 2-O-*acetyl*-β-D-*glucoside* 3 : 4 : 6-*trinitrate*.

Conditions	NaOH added (Equivs. per mole of ester)	NaOH used	NO_2^- formed	Conditions	NaOH added (Equivs. per mole of ester)	NaOH used	NO_2^- formed
15°, 1 hr.	1·0	0·58	—	15°, 1 hr.	Excess	1·27	0·59
,, 2 hr.	1·0	0·60	0·37	,, 2 hr.	,,	1·53	0·67
,, 1 hr.	2·0	0·68	0·43	B. p., 2 hr.	,,	4·80	1·20
,, 2 hr.	2·0	0·86	0·46				
,, 1 hr.	3·0	0·80	0·45				
,, 2 hr.	3·0	1·16	0·53				

Methyl 2 : 3-di-*O*-acetyl-β-D-glucoside 4 : 6-dinitrate (Table 3) and methyl 2-*O*-acetyl-β-D-glucoside 3 : 4 : 6-trinitrate (Table 5) released less inorganic nitrite than did the corresponding di- and tri-nitrates (Tables 2 and 4 respectively). This is presumably due to the

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[7] Bell and Synge, *J.*, 1937, 1711.

[8] O'Meara and Shepherd, *J.*, 1955, 4232.

[9] Baker and Easty, *J.*, 1952, 1208.

unique position of the 6-nitrate group which, in glucopyranosides, is largely protected from the influence of electrophilic substituents in other parts of the molecule.

EXPERIMENTAL

The nitrates were prepared by previous methods.[7, 8] The hydrolyses were carried out in 0·1N-aqueous-methanolic sodium hydroxide as described by Shepherd.[6] In certain experiments (Tables 4 and 5), exactly 1, 2, or 3 mols. of alkali were added.

Isolation of Organic Products.—Hydrolysis of methyl 4 : 6-O-*ethylidene*-β-D-*glucoside* 2 : 3-*dinitrate*. The dinitrate (1·0 g.) was dissolved in methanol (100·0 ml.) and 0·5N-sodium hydroxide (25·0 ml.) was added. After 1 hr. at 22° an aliquot part (1 ml.) was removed for nitrite determination. The excess of alkali was then neutralised with 0·1N-hydrochloric acid, and the mixture concentrated *in vacuo* until crystallisation occurred. The product (0·40 g.) had m. p. 86—87° alone or mixed with the starting material. No other crystalline product could be isolated.

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